REMARKS

With the cancellation of claim 4, claims 1-3, and 5-43 are pending.

The insertion of "less than 5% wt of another famciclovir crystalline form" in claims 1 and 8 is supported by page 7, lines 8-16, of the specification.

The amendment to claim 23 is editorial. Claim 23 as originally filed recites "the famciclovir monohydrate includes the crystalline solid famciclovir of claim 1" meaning that a mixture of the famciclovir monohydrate and the crystalline solid famciclovir of claim 1 is heated in step a) of the process in claim 23. Claim 23 has also been amended to remove multiple dependency. The amendment to claim 43 is also editorial.

The amendments to claims 5, 25-29, 32 and 43 are done to remove improper multiple dependency but the scope of the amended claim recitations is not narrowed.

The amendments to claims 37-42 by inserting "solid" before "pharmaceutical composition" is supported by page 14, lines 16, 18 and 25, of the specification.

Claim Objections

Claims 5, 25-29, 32 and 43 were objected to for improper multiple dependency. These claims have been amended to remove any improper multiple dependency.

Claims 20-22, 24 and 28 were objected to as dependent on a rejected base claim, but were held to contain allowable subject matter. Since the rejected base claim is patentable as explained below, withdrawal of the objection is requested.

Claim Rejections -- 35 U.S.C. 112, Second Paragraph

Applicants respectfully traverse the indefiniteness rejection of claims 18, 19, 23, 26 and 31.

Claims 18 and 19 were rejected as indefinite because the Office Action asserts that "triturated" has several meanings. Applicants would like to point out that "trituration" is defined in page 7, line 23, as referring to a process of mixing a solvent with a solid powder. Thus, applicants submit that, with the definition in page 7, line 23, of the specification, one skilled in the art would have understood the meaning of "triturating" in claims 18 and 19.

Claim 23 has been amended to more clearly recite that the starting material heated in step a) is a mixture of famciclovir monohydrate and crystalline famciclovir Form I.

The Office Action asserts that claim 31 should have "butanol". However, claim 31 already recites that n-butanol is one of the organic solvents that can be used in the process of

claim 31. See also page 11, line 20, of the specification. Thus, applicants submit that claim 31 is not indefinite.

The Office Action rejects claim 26 as indefinite without providing any reason. Applicants assume that claim 26 was rejected as indefinite because it can depend on claim 18, which was rejected as indefinite. Since claim 18 is not indefinite as explained above, the indefinite rejection is believed moot.

Withdrawal of the indefiniteness rejections is requested.

Claim Rejections -- 35 U.S.C. 112, First and Second Paragraphs

Applicants respectfully traverse the rejections of claims 11-17, 33, 34, 36 and 41-43 as indefinite and not enabled. The Office Action alleges that "famciclovir Form III" is unclear because form III is not famciclovir itself. Applicants note that page 7, lines 19-21, discloses that crystalline solid famciclovir form III is a solvate that can be a methanol solvate or ethanol solvate. Page 2, the last line and page 3, lines 1-5 and page 6, lines 19-21, of the application discloses that the present invention relates to 3 novel crystalline forms of famciclovir, designated as forms I, II and III, wherein forms I and II are anhydrous famciclovir and form III is a solvate of famciclovir. Thus, the application of uses the term "crystalline solid famciclovir" to refer to anhydrous or solvate forms of famciclovir crystals. Therefore, a person skilled in the art would have understood form III in claims 11-17, 33, 34, 36 and 41-43 to be related to the solvate form of famciclovir. However, to advance prosecution, claim 11 has been amended to recite "crystalline solid famciclovir solvate".

The Office Action states that it would be extraordinary for two different compounds, i.e., the methanol solvate and ethanol solvate of famciclovir designated as form III, to have the exact same XRD pattern. The Office Action opines that the two versions of form III are clathrates, not hydrates, and that the solvates are not enabled. Applicants respectfully disagree. The two versions of form III disclosed in the application are methanol and ethanol solvates, not hydrates, of famciclovir. The term "clathrate" refers to a substance in which molecules of one compound are enclosed in cavities within another compound. The term "solvate" refers to a substance in which molecules of a solvent are enclosed in the lattice of another compound. Thus, "solvate" can be considered as a type of "clathrate". Page 7, lines 19-21, discloses that the methanol solvate and ethanol solvate of famciclovir designated as form III have the same physicochemical properties and the same XRD pattern. The Office Action opines that there is no evidence to prove that was indeed the case. However, page 7, lines 19-21, of the application is a true statement made based on the experience of the inventors. The XRD patterns of the methanol solvate and ethanol solvate of famciclovir obtained in the invention were indeed the same. Examples 7-9 show that the methanol solvate or ethanol solvate of famciclovir were prepared

using methanol or ethanol, as the solvent. Thus, there is evidence in the application that the methanol solvate and ethanol solvate of famciclovir can be produced using the methods disclosed in the application. Withdrawal of the indefiniteness rejection and non-enablement rejection is requested.

Applicants also respectfully traverse the non-enablement rejection of claims 30 and 35. The Examiner rejected claims 30 and 35 on non-enablement ground because some solvents are used in the processes of both claims. Applicants respectfully note that the organic solvents recited in claim 35 can produce famciclovir monohydrate by containing low levels of water. The organic solvents recited in claim 30 can produce crystalline famciclovir Form I. Thus, applicants respectfully contend that claims 30 and 35 are both enabled.

Applicants also respectfully traverse the non-enablement rejection of claim 35. The Office Action alleges that the preparation of the monohydrate was enabled only with the use of DMF/water (evidently because of what Example 10 shows). However, the Office Action does not put forth any technical reason why the Patent Office doubts the application's disclosure that the use of isopropyl alcohol, ethanol/water, acetone/water, DMA/water, acetonitrile/water, methanol/water, THF/water or isopropyl alcohol/water can form the monohydrate. Example 11 shows that the use of isopropyl alcohol indeed formed the monohydrate. Without being bound by any theory, applicants would like to point out that water molecules can be coming from the moisture in the air to the isopropyl alcohol. There is no technical reason why ethanol/water, acetone/water, DMA/water, acetonitrile/water, methanol/water, THF/water or isopropyl alcohol/water would not form the monohydrate.

Claim Rejections -- 35 U.S.C. §102

(A) Applicants respectfully traverse the anticipatory rejection of claim 35 over Harnden 1990 (*Nucleosides & Nucleotides* (1990) 9:499-513). The Examiner rejected claim 35 because tiny traces of methanol would be expected to be present in the crystallization step of Harnden 1990 and because claim 35 recites "methanol/water mixture" without any limits on the ratio. Harnden 1990 prepared famciclovir by hydrogenation of 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-chloropurine according to the procedure disclosed in Reference 8, followed by crystallization from water to yield famciclovir monohydrate (p. 501, first sentence of the first full paragraph). Reference 8 of Harnden 1990 is Harnden 1989 (*J. Med. Chem.* (1989) 32: 1738-1743). The Examiner relied on page 1741 of Harnden 1989 for the teaching of famciclovir containing traces of methanol. Applicants respectfully disagree that Harnden 1989 teaches famciclovir containing traces of methanol. Near the bottom of page 1741, right column, Harnden 1989 discloses a process of preparing famciclovir by

(a) hydrogenating 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-6-chloropurine in **methanol** containing ammonium formate under reflux for 30 min.'

(b) cooling and filtering;

(c) **removing the solvent**;

(d) taking the residue up in water to form a solution;

(e) **extracting** the solution twice **with chloroform**;

(f) combining the organic layers and drying over $MgSO_4$; and then

(g) **removing the solvent** to afford famciclovir.

Applicants maintain that, in the procedure of Harnden 1989, methanol in step (a) would have been removed in step (c). Whatever little methanol, if any, remaining in the residue of step (c) would not be picked up in the extraction with chloroform in step (e) because methanol is a polar, protic solvent, while chloroform is a non-polar, aprotic solvent. Even if there were traces of methanol remaining in the organic layers in step (f), the traces of methanol would have been removed in step (g). With **removal of the solvent twice** and chloroform extraction, applicants contend that there would have been no methanol in the famciclovir produced at the end of step (g) in the procedure of Harnden 1989. Therefore, when the famciclovir produced in Harnden 1989 was recrystallized from water in the process of Harnden 1990, there would have been no methanol/water mixture to prepare famciclovir monohydrate as done in the process of claim 35. Because Harnden 1990 does not teach every limitation of claim 35, withdrawal of the anticipatory rejection of claim 35 is requested.

(B) Applicants also respectfully traverse the anticipatory rejections of claims 1-10, 18, 19, 31 and 37-43 over Harnden 1989 (*J. Med. Chem.* (1989) 32: 1738-1743); US 5,017,701; US 5,066,805; US 5,138,057; US 6,846,927; US 6,342,603; Freer (*Tetrahedron* (2000) 56:4589-4595); US 6,437,125 and WO 2000/06573.

Harnden 1989 does not disclose crystalline famciclovir form I or II. For a reference to anticipate a claimed invention under the principle of inherency, following the disclosures of the reference must necessarily result in the missing claim limitation. *Schering Corp. v. Geneva Pharmaceutics, Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664 (Fed. Cir. 2003). The crystalline famciclovir form I of claim 1 can be prepared by crystallization from ethyl acetate alone, or ethyl acetate/toluene mixture. The crystalline famciclovir form II of claim 8 can be prepared by crystallization from ethanol or n-butanol. However, Harnden 1989 discloses crystallization of famciclovir from ethyl acetate/hexane mixture to give white shiny plates (p. 1742, left column, top two lines). Harnden 1989 does not disclose using ethyl acetate alone, ethyl acetate/toluene mixture, ethanol or n-butanol to crystallize famciclovir. Following the disclosures of Harnden

1989 would not necessarily result in crystalline famciclovir form I or II. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over Harnden 1989 is requested.

US 5,017,701 or US 6,342,603 does not disclose famciclovir form I or II. US 5,017,701 or US 6,342,603 discloses recrystallization of crude famciclovir from n-butanol (US 6,342,603, Example II-5, column 28, lines 53-54; US 5,017,701, column 7, lines 30-31). Following the disclosures of US 5,017,701 or US 6,342,603 would not necessarily result in crystalline famciclovir form I or II containing less than about 5% of another famciclovir crystalline form. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over US 5,017,701 or US 6,342,603 is requested.

US 5,066,805 does not disclose famciclovir form I or II. In US 5,066,805, crude famciclovir in the form of an oil was purified by column chromatography on silica gel, eluting with 95% chloroform/5% methanol to give famciclovir as a white solid (column 3, lines 30-32). The elution with 95% chloroform/5% methanol from the silica gel column is not the same as crystallization from 95% chloroform/5% methanol. Usually, in column chromatography, after the target analyte is eluted with an eluting solvent, the fractions containing the target analyte collected is dried via evaporation, e.g. by applying vacuum, to remove the eluting solvent. In the working example of US 5,066,805, the elution with 95% chloroform/5% methanol would be followed with evaporation of the 95% chloroform/5% methanol mixture to obtain the white solid. However, unlike cooling a famciclovir solution in chloroform performed in claim 30, evaporating a solution of famciclovir in 95% chloroform/5% methanol would not be expected to yield crystalline famciclovir form I containing less than 5% of another famciclovir crystalline form, or crystalline famciclovir form II containing less than 5% of another famciclovir crystalline form. Following the procedure in US 5,066,805 would not necessarily result in famciclovir form I or II containing less than 5% of another famciclovir crystalline form. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over US 5,066,805 is requested.

US 5,138,057 does not disclose famciclovir form I or II. The Examiner relied on column 8, lines 10-11 and 33, of US 5,138,057 for the disclosures of famciclovir recrystallization from ethyl acetate/diethyl ether and n-butanol. However, column 8, lines 10-11, of US 5,138,057 deals with merely the recrystallization of a dichloropurine intermediate of famciclovir, **not famciclovir**, in ethyl acetate/diethyl ether. Thus, the disclosure in column 8, lines 10-11, of US 5,138,057 is not pertinent to the crystalline famciclovir form I or II. US 5,138,057, column 8, lines 11-12, discloses recrystallization of famciclovir from n-butanol to yield crystalline famciclovir as a colorless solid. However, following the brief description in column 8, lines 32-33, of US 5,138,057 would not necessarily result in crystalline famciclovir form I or II

containing less than 5% of another famciclovir crystalline form. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over US 5,138,057 is requested.

US 6,846,927 does not disclose famciclovir form I or II. In Example 3(a) of US 6,846,927, crude famciclovir was recrystallized from n-butanol, filtered and washed with the mother liquors to yield solid famciclovir (column 2, lines 64-67). The solid famciclovir was then reslurried in n-heptane, filtered and dried at 40° C under vacuum to yield a solid form of famciclovir (column 2, line 67 to column 3, line 2, US 6,846,927). The present invention does not use trituration of solid famciclovir in n-heptane. Following the process in US 6,846,927 would not necessarily result in crystalline famciclovir form II containing less than 5% of another famciclovir crystalline form, or crystalline famciclovir form I containing less than 5% of another famciclovir crystalline form. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over US 6,846,927 is requested.

Freer (*Tetrahedron* (2000) 56:4589-4595) does not disclose crystalline famciclovir form I or II. In page 4595, left column, the second to the last sentence in the first paragraph, Freer discloses recrystallizing crude famciclovir solid from hot isopropanol, filtering, washing with cold isopropanol, and drying under vacuum to yield famciclovir as a white solid. Claim 18 requires triturating anhydrous famciclovir in isopropanol, acetonitrile or diethylether to form crystalline famciclovir form I. Trituration is defined as mixing a solid powder with a solvent, and is different from washing a solid collected on a filter paper with a solvent. In Freer, the recrystallized crude famciclovir solid is filtered and washed with cold isopropanol, which is different from trituration. Thus, claim 18 is not anticipated by Freer. Following the procedure in Freer would not necessarily result in crystalline famciclovir form I containing less than 5% of another form of crystalline famciclovir, or crystalline famciclovir form II containing less than 5% of another form of crystalline famciclovir. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over Freer is requested.

US 6,437,125 does not disclose crystalline famciclovir form I or II. US 6,437,125 discloses recrystallization of crude famciclovir from isopropanol, with the product collected by filtration, washing with isopropanol and dried to yield a famciclovir solid (column 9, lines 43-45. US 6,437,125 does not teach triturating anhydrous famciclovir in isopropanol, acetonitrile or diethylether as recited in claim 18. Thus, claim 18 is not anticipated by US 6,437,125. Following the process in US 6,437,125 would not necessarily result in crystalline famciclovir form I containing less than 5% of another form of crystalline famciclovir, or crystalline famciclovir form II containing less than 5% of another form of crystalline famciclovir. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over US 6,437,125 is requested.

WO 2000/06573 does not disclose crystalline famciclovir form I or II. The Office Action asserts that WO 2000/06573 discloses triturating famciclovir with diethyl ether in Synthesis Example 11. However, Synthesis Example 11 of WO 2000/06573 merely discloses that a white powder was isolated after the **elaboration**, with diethyl ether, of a mixture containing crude anhydrous famciclovir (page 16, lines 7-9; emphasis added). WO 2000/06573 does not disclose trituration of anhydrous famciclovir with diethyl ether because elaboration does not mean trituration. WO 2000/06573 does not anticipate claim 18 because WO 2000/06573 does not disclose triturating anhydrous famciclovir in diethyl ether, isopropanol or acetonitrile. Following the process in WO 2000/06573 would not necessarily result in crystalline famciclovir form I containing less than 5% of another form of crystalline famciclovir, or crystalline famciclovir form II containing less than 5% of another form of crystalline famciclovir. Withdrawal of the anticipatory rejection of claims 1-10, 18, 19 and 31 over WO 2000/06573 is requested.

Page 3 of the Office Action indicates that Brand et al, *Tetrahedron* (1999) 55: 5239-5252, used aqueous acetone to crystallize famciclovir (page 5251, line 1). But page 2 of the Office Action does not reject any claims over Brand et al. Applicants request that the next Office Action explains which claim, if any, is rejected over Brand et al, so that applicants can respond.

Page 4 of the Office Action comments that, concerning claims 37-43, the crystalline form will dissolve if the excipient is water. Applicants note that claims 37-43 have been amended to direct to solid pharmaceutical compositions. Thus, the form of the compositions as claimed are not dissolved in water. Withdrawal of the rejection of claims 37-43 is requested.

In the event that the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee and any other fees that may be required in relation to this paper can be charged to Deposit Account No. 11-0600 referencing Attorney Docket No. 01662/60903.

Respectfully submitted,

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